(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016254 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US2003/025826

(22) International Filing Date: 15 August 2003 (15.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/404,040 16 August 2002 (16.08.2002) US

(71) Applicant *(for all designated States except US)*: **IMMUGEN PHARMACEUTICALS, INC.** [US/US]; 5901 Southwest 87th Street, South Miami, FL 33143 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **TRAVIS, Craig, R.** [US/US]; 5901 Southwest 87th Street, South Miami, FL 33143 (US).

(74) Agents: **HEFNER, Daniel, M.** et al.; Leydig, Voit & Mayer, Ltd., Two Prudential Plaza, Suite 4900, 180 North Stetson, Chicago, IL 60601-6780 (US).

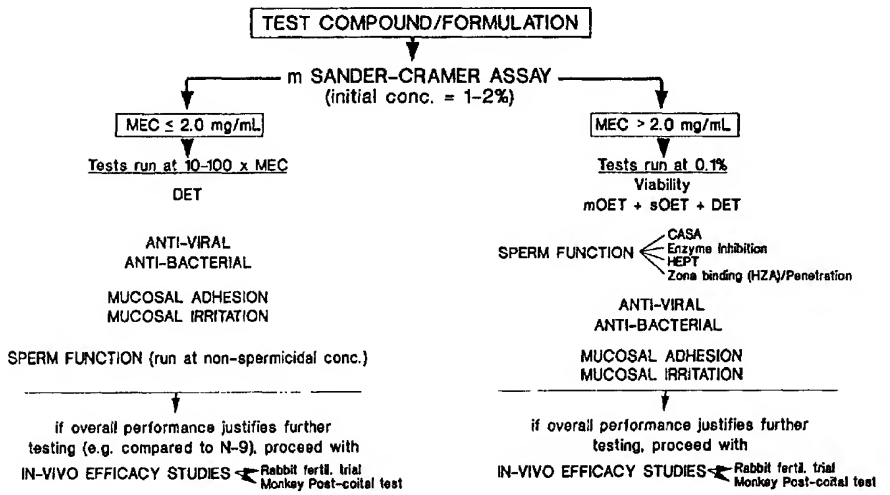
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

[Continued on next page]

(54) Title: CONTRACEPTIVE METHODS AND FORMULATIONS



Chemical Vaginal Contraceptives: Tentative preclinical screening algorithm.
m: modified. MEC: minimum effective concentration. DET: double-end test. sOET: simultaneous one-end test. mOET: modified one-end test. CASA: computer-assisted semen analysis. HEPT: hamster-egg penetration test. HZA: hemizona assay.

(57) Abstract: The present invention provides a method of contraception involving applying at least one 5'-alkyl resorcinol and/or cannabinoid (e.g., cannabinol derivative (including, but not limited to, tetrahydrocannabinols), cannabidiol derivative, cannabigerol derivative, etc.) to an individual in an amount and at a location sufficient to prevent pregnancy. The invention also provides formulations particularly useful as a barrier contraceptive comprising at least one 5'-alkyl resorcinol and/or cannabinoid.

WO 2004/016254 A2

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

CONTRACEPTIVE METHODS AND FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to United States Provisional Patent Application No. 60/404,040, filed August 16, 2003.

FIELD OF THE INVENTION

The present invention is directed to the use of cannabinoids and alkylresorcinols as contraceptives.

BACKGROUND OF THE INVENTION

Overpopulation is clearly the greatest threat to mankind's existence. Unprotected sexual activity can not only lead to unwanted pregnancies but to the transmission of sexually transmitted diseases (STDs), the most feared of which is HIV-1. The use of oral contraceptives can prevent pregnancy but not the transmission of STDs. Moreover, the use of oral contraceptives is not without risk. For example, there is a clear correlation between the use of oral contraceptives and a risk of thromboembolism, which is especially increased for smokers and those women with hypertension[1]. Another study showed a two fold increased risk for stroke with contraceptive use compared with no use, which increased even more in combination with the presence of smoking, hypertension, hypercholesterolemia, or obesity [2]. For these reasons, the use of oral contraceptives becomes less attractive to women especially those who engage in occasional sexual activity.

The use of a barrier contraceptive such as a condom can prevent both pregnancy and STDs but require cooperation of the male partner and its lack of acceptance is without doubt its failing. Moreover, it has been demonstrated that detergent spermicide, such as nonoxynol-9 (N-9) can actually increase the risk of HIV transmission. As such there is a need for an agent(s) that are not associated with irritation or ulceration of either the cervicovaginal or penile epithelium that will serve as a topical contraceptive and microbicide if both the problem of overpopulation and the transmission of STDs disease are to be limited.

SUMMARY OF THE INVENTION

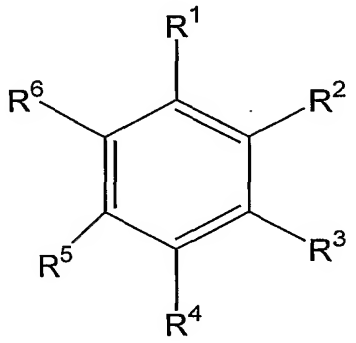
The present invention provides a method of contraception involving applying at least one 5'-alkyl resorcinol and/or cannabinoid (e.g., cannabinol derivative (including, but not limited to, tetrahydrocannabinols), cannabidiol derivative, cannabigerol derivative, etc.) to an individual in an amount and at a location sufficient to prevent pregnancy. The invention also provides formulations particularly useful as a barrier contraceptive comprising at least one 5'-alkyl resorcinol and/or cannabinoid.

DESCRIPTION OF THE FIGURES

Figure 1 is a flow chart for preclinical evaluation.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of contraception comprising applying at least one 5'-alkyl resorcinol and/or cannabinoid to an individual in an amount and at a location sufficient to prevent pregnancy, such as to the genital tissue of such patient. In one embodiment, at least one compound within the pharmacologically-acceptable composition can be a resorcinol derivative (e.g., a 5-alkyl or 3-alkyl or -acyl resorcinol). Such compounds are advantageous for use in the inventive method as they generally exhibit low cytoxicity (see, e.g., U.S. Patents 5,859,067, 6,274,635, and 6,566,560). Exemplary resorcinols can have the following formula:



Formula I

wherein,

R^1, R^3, R^5, and R^6 can optionally be $-COR^1$, $-COR^3$, $-COR^5$, and/or $-COR^6$, respectively, and preferably R^3 is $-COR^3$, and wherein R can otherwise be as follows:

R^1 is: a) H,

b) a C_{1-4} alkyl group or ester thereof,

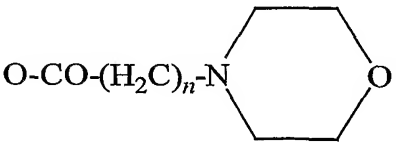
c) COOH,

d) OH,

e) a O-C_{1-5} alkyl (preferably OCH_3) or alkanoyl, optionally substituted by mono- or di- methylamino or ethylamino groups,

f) a O-CO-C_{3-10} alkyl group containing a carboxyl or amino group,

g)



wherein n = 1 to 8

h) a p-aminobenzyl group or a C_{1-7} aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

i) R^1 and R^2 comprise a substituent of the formula $-O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen (e.g., fluorine, bromine, iodine, astatine);

j) a lactone (e.g., COCOH); or

k) $CH(CH_3)CO_2H$ or $-OCOCH_3$

R^2 is: a) H, OH, COOH, or a halogen

b) C_{1-6} carboxy or alkoxy group, or

c) R^1 and R^2 comprise a substituent of the formula $-O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R^3 is: a) $(W)_m$-Y-$(Z)_n$, wherein

W is a C_{5-12} straight or branched (preferably 1S'CH_3, 2R'CH_3 dimethyl) alkyl (e.g., -pentyl, -hexyl, -heptyl, -octyl, or –nonyl), alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen (e.g., halogen terminal group or even dihalogen),

Y is a bond, O, S, SO, SO_2, CO, NH, N(C_{1-6} alkyl), or NCS,

Z is: i) a C_{5-12} alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN_{1-3}, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}\text{ alkyl})_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, CN, CF_3, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}\text{ alkyl})_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

b) a C_{5-12} alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$

alkyl, or CON(C_{1-4} alkyl)$_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

c) a C_{5-12} alkene or alkyne group, optionally substituted with a halogen, dithiolene, terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or CON(C_{1-4} alkyl)$_2$,wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different;

R^4 is: a) H or halogen (preferably bromine)

b) OH, or

c) C_{1-6} alkoxyl or carboxyl;

R^5 is a) H,

b) a C_{1-4} alkyl group,

c) COOH,

d) OH, or OCH_3,

e) a O-C_{1-5} alkyl (ether) or alkanoyl, optionally substituted with at least one mono- or di- methylamino or ethylamino group, or

f) a lactone; and

R^6 is: a) H or OH;

b) C_{1-4} alkyl (preferably ethyl), alkenyl, alkynyl, group, or mixture thereof,

c) O-C_{1-4} alkyl, alkenyl, alkynyl, group, or mixture thereof, or

d) a pryenyl, gerenyl, or farnesyl group, optionally substituted at any position with one or more halogens,

e) $(W)_m$-Y-$(Z)_n$, wherein

W is a C_{5-12} alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO_2, CO, NH, N(C_{1-6} alkyl), or NCS,

Z is: i) a C_{5-12} alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN_{1-3}, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or CON(C_{1-4} alkyl)$_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, CN, CF_3, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or CON(C_{1-4} alkyl)$_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

f) a C_{5-12} alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different,

g) a C_{5-12} alkene or alkyne group, optionally substituted with a halogen, dithiolene, terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$,wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

h) $CH(CH_3)CO_2H$, CH_2COOH, or $-OCOCH_3$.

Compounds according to Formula I preferably include a lactone, H, OH or OCH_3, $-CH(CH_3)CO_2H$, or $-OCOCH_3$ as R^1 substituents. Preferred substituents at R^2 are hydrogen, halogen (most preferably fluorine) hydroxyl, COOH, or methoxyl groups. Preferred substituents at R^4 include H or a halogen (most preferably bromine). Preferred substituents at R^5 include a lactone, H, OH, and OCH_3. Preferred substituents at R^6 include H, OH, ethyl, $CH(CH_3)CO_2H$, CH_2COOH, and $-OCOCH_3$. Where compounds of formula I are included, preferably R^6 is methyl or ethyl. A more preferred compound according to Formula I has hydroxyl substituents at R^1, R^5, and a methyl substituent at R^6; even more preferably, the compound has a third hydroxyl substituent at R^2. Preferred substituents at R^3 are discussed elsewhere herein; however, the invention provides compounds according to Formula I, wherein R^3 is:

a) $(W)_m$-Y-$(Z)_n$, wherein

W is a C_{5-12} alkyl, alkenyl, alkynyl (e.g., 2'-ynyl, 3'-ynyl or 4'-ynyl), group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO2, CO, NH, N(C_{1-6} alkyl), or NCS,

Z is: i) a C_{5-12} alkyl, alkenyl, alkynyl (e.g., 2'-ynyl, 3'-ynyl or 4'-ynyl), group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN_{1-3}, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C1-6 alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, CN, CF_3, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different,

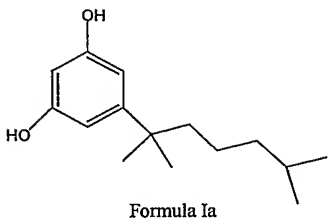
wherein at least one of W and Z includes a branched chain and wherein *m* and *n* are the same or different, and each is either 0 or 1,

b) a terminally-branched (e.g., terminal dimethyl) C_{5-12} alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-}

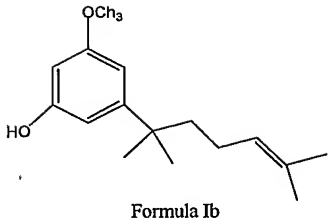
$_4$ alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

c) a terminally-branched C_{5-12} alkene or alkyne group, optionally substituted with a halogen, dithiolene, terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$,wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different.

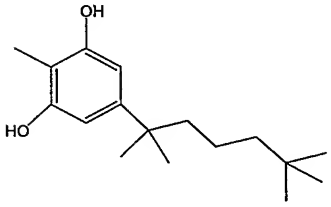
Particularly preferred R^3 substituents include C_5-C_{12} alkynes, and particularly preferred groups also include di- or tri-methyl terminal groups. A most preferred substituent at R^3 is a dimethylheptyl, particularly 1'S, 2'SR, and also preferably with terminal halogen (or dihalogen) substituents, and another preferred substituent is 5,5-diimethyl hex(1-ene)(3-yne)yl (e.g., compound Ii). Many such compounds exhibit antineoplastic activity and can be employed as such, as described herein. While any such compounds can be included within the composition in accordance with the inventive method, some preferred compounds are as follows:



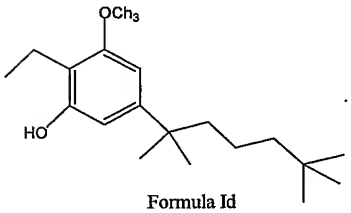
Formula Ia



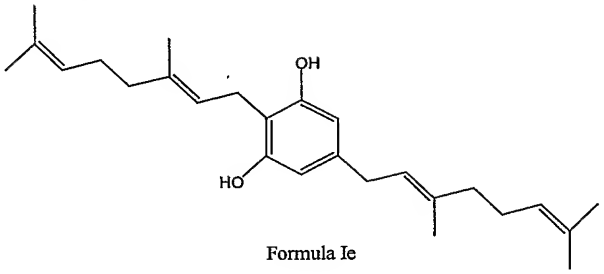
Formula Ib



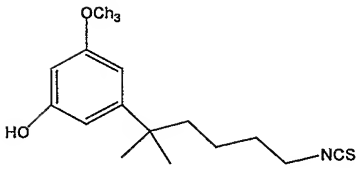
Formula Ic



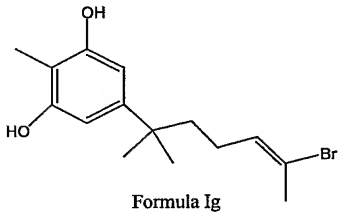
Formula Id



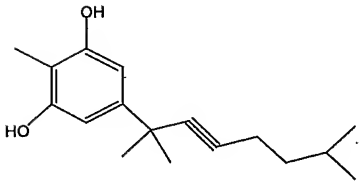
Formula Ie



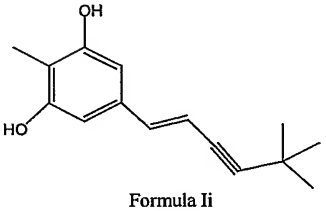
Formula If



Formula Ig

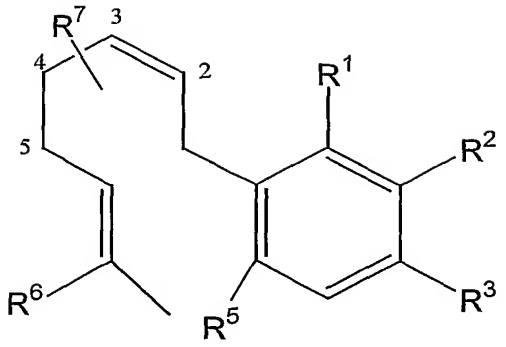


Formula Ih



Formula Ii

As mentioned, compounds according to Formula I can have gerenyl substituents at R^6. In this regard, at least one compound within the pharmacologically-acceptable composition can be cannabigerol or a derivative thereof having the following formula:



Formula II

wherein:

R^1 is: a) H,

b) a C_{1-4} alkyl group or ester thereof,

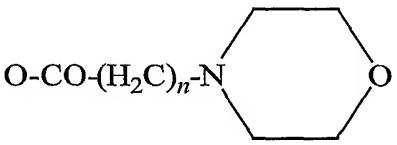
c) COOH,

d) OH,

e) a O-C_{1-5} alkyl (preferably OCH_3) or alkanoyl, optionally substituted by mono- or di- methylamino or ethylamino groups,

f) a O-CO-C_{3-10} alkyl group containing a carboxyl or amino group,

g)



wherein $n = 1$ to 8

h) a p-aminobenzyl group or a C_{1-7} aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

i) R^1 and R^2 comprise a substituent of the formula -$O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen;

j) a lactone (e.g., COCOH); or

k) $CH(CH_3)CO_2H$ or $-OCOCH_3$

R^2 is: a) H, OH, COOH, or a halogen

b) C_{1-6} carboxy or alkoxy group, or

c) R^1 and R^2 comprise a substituent of the formula -$O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded,

comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R^3 is: a) $(W)_m$-Y-$(Z)_n$, wherein

W is a C_{5-12} straight or branched (preferably 1S'CH_3, 2R'CH_3 dimethyl) alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO_2, CO, NH, N(C_{1-6} alkyl), or NCS,

Z is: i) a C_{5-12} alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN_{1-3}, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, CN, CF_3, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

b) a C_{5-12} alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

c) a C_{5-12} alkene or alkyne group, optionally substituted with a halogen, dithiolene, terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$,wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different;

R^5 is a) H,

b) a C_{1-4} alkyl group,

c) COOH,

d) OH, or OCH_3,

e) a O-C_{1-5} alkyl (ether) or alkanoyl, optionally substituted with at least one mono- or di- methylamino or ethylamino group, or

f) a lactone; and

R^6 is:

a) hydrogen,

b) C_{1-6} alkoxy , C_{1-6} alkylthio, C_{1-6} alkyl (preferably ethyl), or C_{1-6} haloalkyl,

c) CN,
d) CO_2H,
e) CO_2-C_{1-4} alkyl,
f) C(Y)(Z)-OH,
g) C(Y)(Z)-O-C_{1-4} alkyl, or
h) C_{1-6} alkyl-CO_2-Y,
wherein Y and Z are each independently H or C_{1-6} alkyl,

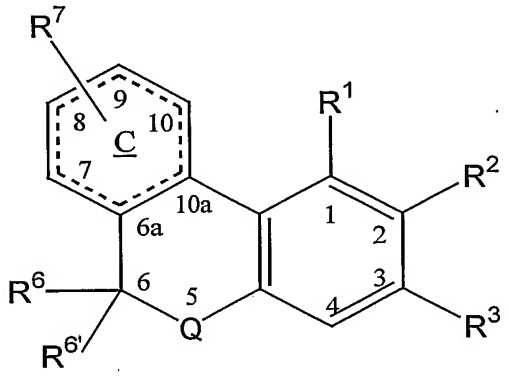
R^7 is: a) hydroxy (preferably β-hydroxy) or lactone,
b) halo,
c) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,
d) CN,
e) N_3,
f) CO_2H,
g) CO_2-C_{1-4} alkyl,
h) C(Y)(Z)-OH,
i) C(Y)(Z)-O-C_{1-4} alkyl,
j) C_{1-6} alkyl-CO_2-Y, or
k) =O or =S,

wherein Y and Z are each independently H or C_{1-6} alkyl, and wherein R^7 can be at any of positions 2-5.

Compounds according to Formulas I and II can be synthesized using known procedures from commercially available starting materials (see, e.g., Dominianni et al., *J. Org. Chem., 42*, 344-46 (1977); Baek et al., *Arch. Pharm. Res., 19*, 228-30 (1996); Guthrie et al., *J. Org. Chem. 47*, 2369-76 (1982)). For example, acid catalyzed condensation of 2,6-dimethoxyphenol with OH-R^3 can produce a 4-alkylphenol intermediate. Conversion of the phenolic group to the diethylphosphate ester followed by reduction with lithium metal in liquid ammonia can then produce a dimethoxybenzene derivative. Mono- or didemethylation of this compound (e.g., with boron tribromide) can then yield the desired methoxyphenol and/or resorcinol (Formula I), respectively. Compounds of Formula I having alkyl substituents at R^6 can be prepared, for example, first by lithiation of the dimethoxybenzene derivative at R^6 (e.g., in the presence of Bu/THF) and subsequent exposure to an alkylating agent (e.g., methyl or ethyl iodide or sulfate). Mono- or didemethylation of this compound (e.g., with boron tribromide) can then yield the desired methoxyphenol and/or resorcinol (Formula I), respectively, having the alkyl substituents at R^6. Compounds of Formula II can be prepared, for example, by acid catalyzed condensation of a methoxyphenol and/or resorcinol (Formula I) having a desired substituents at R^3 with geraniol (e.g., in the presence of BF_3, Et_2O, silica, and

CH_2Cl_2). Of course, these compounds can be synthesized by other appropriate methods, many of which are known in the art.

In another embodiment, at least one compound within the pharmacologically-acceptable composition is a cannabinol derivative having the following formula:



Formula III

wherein,

R^1 is: a) H,

b) a C_{1-4} alkyl group or ester thereof,

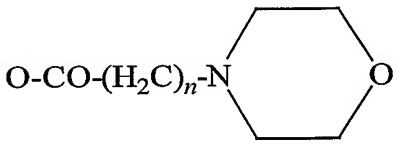
c) COOH,

d) OH,

e) a O-C_{1-5} alkyl (preferably OCH_3) or alkanoyl, optionally substituted by mono- or di- methylamino or ethylamino groups,

f) a O-CO-C_{3-10} alkyl group containing a carboxyl or amino group,

g)



wherein n = 1 to 8

h) a p-aminobenzyl group or a C_{1-7} aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

i) R^1 and R^2 comprise a substituent of the formula -$O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen;

j) a lactone (e.g., COCOH); or

k) $CH(CH_3)CO_2H$ or $-OCOCH_3$

R^2 is: a) H, OH, COOH, or a halogen

b) C_{1-6} carboxy or alkoxy group, or

c) R^1 and R^2 comprise a substituent of the formula $-O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R^3 is: a) $(W)_m$-Y-$(Z)_n$, wherein

W is a C_{5-12} straight or branched (preferably 1S'CH_3, 2R'CH_3 dimethyl) alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO_2, CO, NH, N(C_{1-6} alkyl), or NCS,

Z is: i) a C_{5-12} alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN_{1-3}, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, CN, CF_3, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

b) a C_{5-12} alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

c) a C_{5-12} alkene or alkyne group, optionally substituted with a halogen, dithiolene, terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$,wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different;

R^6 and $R^{6'}$ together form =O or =S, or each is independently selected from the group consisting of:

a) hydrogen,

b) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,

c) CN,

d) CO_2H,

e) CO_2-C_{1-4} alkyl,
f) C(Y)(Z)-OH,
g) C(Y)(Z)-O-C_{1-4} alkyl, and
h) C_{1-6} alkyl-CO_2-Y,
wherein Y and Z are each independently H or C_{1-6} alkyl,

R^7 is: a) hydroxy or lactone,
b) halo,
c) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,
d) CN,
e) N_3,
f) CO_2H,
g) CO_2-C_{1-4} alkyl,
h) C(Y)(Z)-OH,
i) C(Y)(Z)-O-C_{1-4} alkyl,
j) C_{1-6} alkyl-CO_2-Y, or
k) =O or =S,
wherein Y and Z are each independently H or C_{1-6} alkyl;

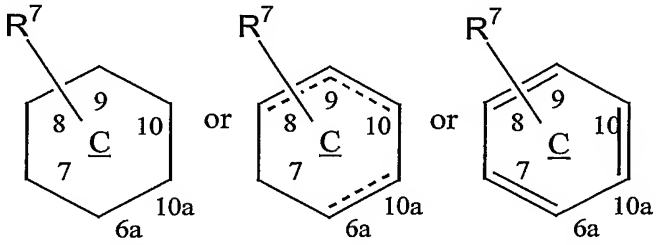
Q is: a) O or S, or
b) N-W, wherein W is:
i) hydrogen,
ii) C_{1-6} alkoxyalkyl, C_{1-6} alkyl, or C_{1-6} haloalkyl
iii) OC_{1-6} alkyl, or OC_{1-6} haloalkyl,
iv) CN,
v) C_{1-6} alkyl,
vi) C(Y)(Z)C_{1-4} alkyl, or
vii) C_{1-6} alkyl-CO_2-Z,
wherein Y and Z are each independently H or C_{1-6} alkyl.

Preferably R^1 in Formula III is H, O-C_{1-4} alkyl (more preferably methoxy) or a hemi ester of succinic acid, malonic acid or the alaninate ester of alanine and salts thereof. In another preferred embodiment, R^1 and R^2 together comprise a substituent of the formula -O(CH_2)$_{3-5}$-, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprise a ring where at least one hydrogen atom thereof is optionally substituted with a halogen (e.g., an O,2 propano ring). Furthermore, where R^2 Formula III is a halogen, preferably it is iodo. Preferably, R^6 and $R^{6'}$ together form =O or each are methyl, ethyl, or methoxy.

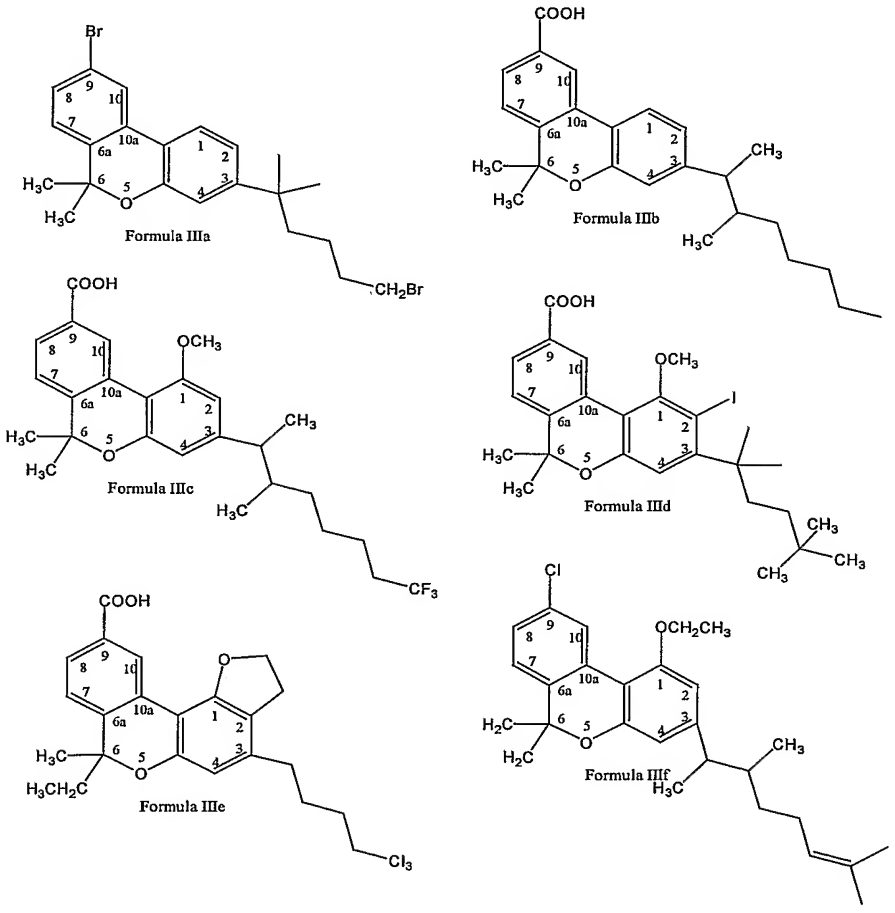
While R^7 can be at any of positions 7-10 of ring C, preferably it is at position 9 of the ring. Also, in some embodiments, R^7 preferably is electronegative (e.g., COOH,

halogen, β-hydroxy, or lactone.), while in others, it can be substituted with either a lactone or a β-hydroxy group.

Ring C in Formula III can be any of the following (the dashed lines representing a double bond at either the Δ6a-10a, Δ8-9, or Δ9-10 position):



However, preferably the ring is aromatic. In such compounds, R^7 preferably is electronegative and more preferably is on C9. Furthermore, for such embodiments, R^1 preferably is other than OH and preferably is deoxy, an ester, or an ether. Exemplary cannabinol derivative compounds include:



Another preferred compound according to Formula III is a derivative of delta-8 tetrahydrocannabinol, in which R1 is an acetate, R6 is a lactone, and R7 is COOH

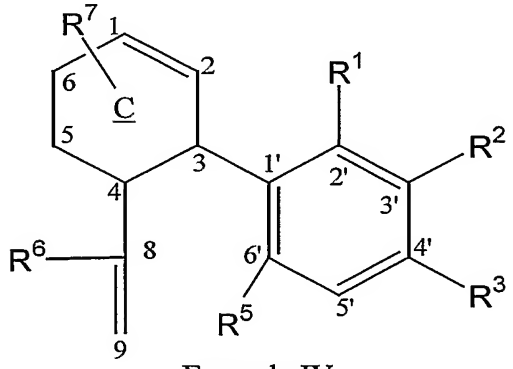
(exemplary species of which are described, for example, in Rhee et al. *J. Med. Chem.,* 40, 3228-33 (1997)).

Many compounds according to Formula III are well known, and others can be manufactured in accordance with published methods (see, for example, International Patent Application WO99/20268 (Burstein), and U.S. Patents 2,509,386 (Adams), 3,799,946 (Loev), 3,856,821 (Loev), 3,897,306 (Vidic et al.), 4,064,009 (Fukada et al.), 4,087,545 (Archer et al.), 4,142,139 (Bindra), 4,309,545 (Johnson), 4,599,327 (Nógrádi et al.), 4,833,073 (McNally et al.), 4,876,276 (Mechoulan et al.), 4,973,603 (Burstein), 5,338,753 (Burstein et al.), 5,389,375 (ElSohly), 5,440,052 (Makriyannis et al.), 5,605,906 (Lau), and 5,635,530 (Mechoulam et al.); and Charalambous et al., *Pharm. Biochem. Behav., 40*, 509-12 (191), Gareau et al., *Bioorg. Med. Chem. Lett., 6*(2), 189-94 (1996), Griffin et al., *Br. J. Pharmacol., 126*, 1575-84 (1999), Huffman et al., *Bioorg. Med. Chem. Lett., 6*, 2281-88 (1998), Lemberger et al., *Clin. Pharmacol. Ther., 18*(6), 720-26 (1975), Loev et al., *J. Med. Chem., 16*(11), 1200-06 9 (1973), Loev et al., *J. Med. Chem., 17*(11), 1234-35 (1974), Martin et al., *Pharm. Biochem. Behav., 46*, 295-301 (1993), Papahatjis et al., *J. Med. Chem., 41*(7), 1195-1200 (1998), Pars et al., *J. Med. Chem., 19*(4), 445-53 (1976), Pertwee et al., *Pharmacol. Ther., 74(*2), 129-80 (1997), Razdan et al., *J. Med. Chem., 19*(4), 454-60 (1976), Razdan, *Pharmacol. Reviews, 38*(2) 75-149 (1980), Reggio et al., *J. Med. Chem., 40*(20), 3312-18 (1997), Reggio et al., *Life Sci., 56*(23/24), 2025-32 (1995), (Ross et al., *Br. J. Pharmacol., 126*, 665-72 (1999), Thomas et al., *J. Pharm. Exp. Ther., 285*(1), 285-92 (1998), Wiley et al., *J. Pharm. Exp. Ther., 285*(1), 995-1004 (1998), Winn et al., *J. Med. Chem., 19*(4), 461-71 (1976), and Xie et al., *J. Med. Chem., 41*, 167-74 (1998)).

In the preferred embodiment wherein ring C of Formula III is aromatic, such compounds additionally can be manufactured by aromatizing an appropriate tetrahydrocannabinol (THC) derivative molecule by known methods (see, e.g., Adams et al., *J. Am. Chem. Soc., 62*, 23401 (1940); Ghosh et al., *J. Chem. Soc.*, 1393 (1940); and Adams et al., *J. Am. Chem. Soc., 70*, 664 (1948)). For example, aromatization of such compounds can occur by heating the compound with sulfur at about 238-240 °C, under a nitrogen atmosphere, for about 4 hours (Rhee et al., *J. Med. Chem., 40*(20), 3228-33 (1997)). Other suitable methods include aromatization using a catalyst (e.g., palladium on carbon) or a chemical dehydrogenating agent (e.g., 2,3-dichloro-5,6-dicyanoquinone) (see, for example, U.S. Patent 3,799,946 (Loev)).

As mentioned, in some applications of the inventive method, particularly where at least one of the compounds within the composition is a cannabinol derivative, it is desirable to mitigate potentially deleterious psychoactivity attributed to some such compounds. As an alternative to employing non-psychoactive cannabinol derivatives (e.g., selective CB2 agonists) within the composition, other pharmacologically-active

agents can be employed in addition to mitigate psychoactive effects. For example, as some of the aforementioned compounds might exert some activity on CB1 receptors, it is often desirable to adjunctively administer a selective CB1 antagonist to the patient. Indeed, in some applications it is desired to co-administer a non-selective CB2 agonist (e.g., Δ8- or Δ9-THC and derivatives thereof) in small doses, in which cases administration of a CB1 antagonist is preferred. Many suitable selective CB1 antagonists are known in the art (Rinaldi-Carmona et al., *FEBS Lett., 350*, 240-44 (1994), see also U.S. Patents 5,624, 941 (Barth et al.), 5,747,524 (Cullinan et al.), 5,925,768 (Barth et al.)). SR-1241716A is a particularly potent, and theretofore preferred, selective CB1 antagonist for use in the inventive method. Other preferred selective CB1 antagonists are cannabidiol and its derivatives (see, e.g., U.S. Patent 2,304,669 (Adams); Razdan et al., *Pharmacol. Reviews, 38*(2), 75-149 (1986); Reggio et al., *Life Sci., 56*(23-24), 2025-32 (1995)), as these potently antagonize the CB1 receptor. In addition to antagonizing CB1, cannabidiol and many of its derivatives also advantageously attenuate the cytochrome P_{450} system in the liver, leading to enhanced bioavailability of other compounds within the composition (e.g., Bornheim et al., *Chem. Res. Toxicol., 11*, 1209-16 (1998)). In this regard, in some embodiments of the inventive method, at least one compound within the pharmacologically-acceptable composition is cannabidiol or a derivative thereof having the following formula:



Formula IV

wherein:

R^1 is: a) H,

b) a C_{1-4} alkyl group or ester thereof,

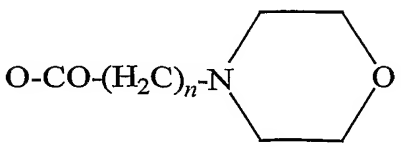
c) COOH,

d) OH,

e) a O-C_{1-5} alkyl (preferably OCH_3) or alkanoyl, optionally substituted by mono- or di- methylamino or ethylamino groups,

f) a O-CO-C_{3-10} alkyl group containing a carboxyl or amino group,

g)



wherein n = 1 to 8

h) a p-aminobenzyl group or a C_{1-7} aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

i) R^1 and R^2 comprise a substituent of the formula $-O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen;

j) a lactone (e.g., COCOH); or

k) $CH(CH_3)CO_2H$ or $-OCOCH_3$

R^2 is: a) H, OH, COOH, or a halogen

b) C_{1-6} carboxy or alkoxy group, or

c) R^1 and R^2 comprise a substituent of the formula $-O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R^3 is: a) $(W)_m$-Y-$(Z)_n$, wherein

W is a C_{5-12} straight or branched (preferably 1S'CH_3, 2R'CH_3 dimethyl) alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO_2, CO, NH, N(C_{1-6} alkyl), or NCS,

Z is: i) a C_{5-12} alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN_{1-3}, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, CN, CF_3, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

b) a C_{5-12} alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

c) a C_{5-12} alkene or alkyne group, optionally substituted with a halogen, dithiolene, terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$,wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different;

R^5 is a) H

b) a C_{1-4} alkyl group

c) COOH

d) OH, or

e) a O-C_{1-5} alkyl (ether) or alkanoyl, optionally substituted with at least one mono- or di- methylamino or ethylamino group;

R^6 is:

a) hydrogen,

b) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,

c) CN,

d) CO_2H,

e) CO_2-C_{1-4} alkyl,

f) C(Y)(Z)-OH,

g) C(Y)(Z)-O-C_{1-4} alkyl, or

h) C_{1-6} alkyl-CO_2-Y,

wherein Y and Z are each independently H or C_{1-6} alkyl,

R^7 is: a) hydroxy or lactone,

b) halo,

c) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, C_{1-6} carboxy, or C_{1-6} haloalkyl,

d) CN,

e) N_3,

f) CO_2H,

g) CO_2-C_{1-4} alkyl,

h) C(Y)(Z)-OH,

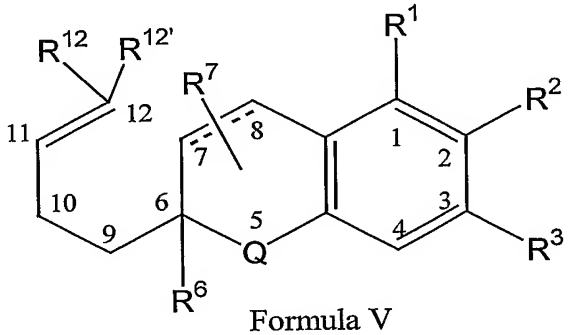
i) C(Y)(Z)-O-C_{1-4} alkyl,

j) C_{1-6} alkyl-CO_2-Y, or

k) =O or =S,

wherein Y and Z are each independently H or C_{1-6} alkyl, and wherein R^7 can be at any of positions 1, 2, 5, or 6 of ring C.

Another preferred compound for use in the inventive method is a cannabichromene derivative having the following formula:



Formula V

wherein,

R^1 is: a) H,

b) a C_{1-4} alkyl group or ester thereof,

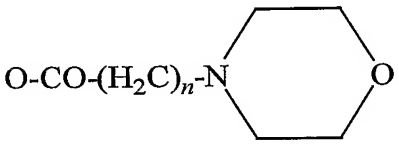
c) COOH,

d) OH,

e) a O-C_{1-5} alkyl (preferably OCH_3) or alkanoyl, optionally substituted by mono- or di- methylamino or ethylamino groups,

f) a O-CO-C_{3-10} alkyl group containing a carboxyl or amino group,

g)



wherein n = 1 to 8

h) a p-aminobenzyl group or a C_{1-7} aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

i) R^1 and R^2 comprise a substituent of the formula -$O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen;

j) a lactone (e.g., COCOH); or

k) $CH(CH_3)CO_2H$ or $-OCOCH_3$

R^2 is: a) H, OH, COOH, or a halogen

b) C_{1-6} carboxy or alkoxy group, or

c) R^1 and R^2 comprise a substituent of the formula $-O(CH_2)_{3-5}$, wherein R^1 and R^2, together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R^3 is: a) $(W)_m$-Y-$(Z)_n$, wherein

W is a C_{5-12} straight or branched (preferably 1S'CH_3, 2R'CH_3 dimethyl) alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO_2, CO, NH, N(C_{1-6} alkyl), or NCS,

Z is: i) a C_{5-12} alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN_{1-3}, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, CN, CF_3, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

b) a C_{5-12} alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different, or

c) a C_{5-12} alkene or alkyne group, optionally substituted with a halogen, dithiolene, terminal aromatic ring, CN_{1-3}, NCS, CO_2H, or CO_2C_{1-4} alkyl, $CONH_2$, $CONHC_{1-4}$ alkyl, or $CON(C_{1-4}$ alkyl$)_2$,wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different;

R^6 is selected from the group consisting of:

a) hydrogen,

b) hydroxy or lactone,

c) halo,

d) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,

e) CN,

f) N_3,

g) CO_2H,

h) CO_2-C_{1-4} alkyl,

i) C(Y)(Z)-OH,
j) C(Y)(Z)-O-C_{1-4} alkyl, and
k) C_{1-6} alkyl-CO_2-Y,
wherein Y and Z are each independently H or C_{1-6} alkyl,

R^7 is selected from the group consisting of:
a) hydrogen,
b) hydroxy or lactone,
c) halo,
d) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,
e) CN,
f) N_3,
g) CO_2H,
h) CO_2-C_{1-4} alkyl,
i) C(Y)(Z)-OH,
j) C(Y)(Z)-O-C_{1-4} alkyl,
k) C_{1-6} alkyl-CO_2-Y, and
l) =O or =S;
wherein Y and Z are each independently H or C_{1-6} alkyl,

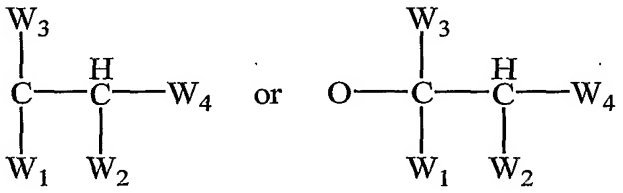
R^{12} and $R^{12'}$ together form =O or =S, or each is independently selected from the group consisting of:
a) hydrogen,
b) hydroxy or lactone,
c) halo,
b) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,
c) CN,
d) N_3,
d) CO_2H,
e) CO_2-C_{1-4} alkyl,
f) C(Y)(Z)-OH,
g) C(Y)(Z)-O-C_{1-4} alkyl, and
h) C_{1-6} alkyl-CO_2-Y,
wherein Y and Z are each independently H or C_{1-6} alkyl,

Q is: a) O or S, or
b) N-W, wherein W is:
i) hydrogen,
ii) C_{1-6} alkoxyalkyl, C_{1-6} alkyl, or C_{1-6} haloalkyl
iii) OC_{1-6} alkyl, or OC_{1-6} haloalkyl,
iv) CN,

v) C_{1-6} alkyl,
vi) $C(Y)(Z)C_{1-4}$ alkyl, or
vii) C_{1-6} alkyl-CO_2-Z,
wherein Y and Z are each independently H or C_{1-6} alkyl.

Many cannabichromene derivatives are known, and others can be synthesized using methods that are known in the art (see, e.g., U.S. patent 4,315,862).

In addition to having the indicated substituents, R^3 in any of formulas I-V preferably is:



wherein W_1 is H, methyl, or ethyl, wherein W_2 and W_3 are each independently H or methyl, wherein at least one of W_1, W_2, and W_3 is other than H and/or halogenated, and wherein W_4 is a C_{1-4} alkyl or haloalkyl, optionally substituted with an aromatic ring. Preferably, R^3 is a branched C_{6-12} alkyl group containing at least one double bond (more preferably at position C_4-C_{10}), and preferably the chain has an odd number of carbon atoms. More preferably, R^3 is terminally branched or contains a terminal double bond, and the invention provides compounds according to Formulas I-V having such substituents. More preferably, R^3 preferably is dimethylheptyl (DMH) (e.g., 1',1' DMH or 1'R, 2'S DMH), dimethylhexyl, or dimethylpentyl. For example, R^3 can be a di- tri- or tetramethylpentyl, -hexyl, or -heptyl, etc., chain (e.g., 1,1,5-trimethylhexyl, 1,1,5,5-tetramethylhexyl, or 1,1,5-trimethyl-hept-4-enyl). In some instances, the R^3 substituent can have bulky terminal moieties, for example, methyl, dimethyl, $(CH_2)_{1-6}$-CON(CH3)2, or C6-12 haloalkyl with halogenated terminal carbon atoms (preferably bromine, fluorine and iodine).

In the context of this invention, halogenated alkanes, alkenes, and alkynes can have any number of halogen substitutions. In a preferred embodiment, the halogenated alkane, alkene, or alkyne has at least one halogen on a terminal carbon atom (e.g., CX_{1-3}, wherein X is halogen). Alkyl groups (as well as alkenes and alkynes) can be straight chain or branched. Moreover, the compounds can exist as a single stereoisomer or a mixture of stereoisomers (e.g., a racemic mixture), or a single geometric isomer (e.g., E, Z, cis or trans) or a mixture of geometric isomers, all of which are within the scope of the invention.

In practice, the method comprises applying one or more of the 5'-alkyl resorcinol and/or cannabinoid compounds to an individual in an amount and at a location sufficient to prevent pregnancy. Typically, the compound is applied to genital tissue, and the invention contemplates application to either penile or vaginal tissue, and preferably both, to maximally guard against the risk of unwanted pregnancy. Typically, the 5'-alkyl resorcinol and/or cannabinoid compounds are delivered in a concentration of from about 1 to about 1000 μM/ml, and more preferably between about 10 to 100 μM/ml, such as between about 25 to about 75 μM/ml.

To effectively deliver the 5'-alkyl resorcinol and/or cannabinoid compounds, they can be formulated in any desirable manner for topical application to the desired tissue. For example, the compound(s) can be formulated into a solution or suspension (e.g., in water or oil) or in a gel, cream, salve, or other fluid or semi-fluid formulation suitable for topical application. Alternatively, the compounds can be formulated into a composition to be used in conjunction with other contraceptive devices, preferably barrier devices (e.g., condoms, sponges, diaphragms, etc.). Methods of formulating contraceptive compositions for use alone or in conjunction with such barrier devices are well-known in the art, and any of them can be employed as desired.

Desirably, a composition for use in the inventive method, has a viscosity and make-up that will not interfere with the sexual encounter and yet provide the appropriate protection against fertilization. Such a composition desirably is neither be granular nor syrupy, and it is also desirable for the composition not to appreciably change consistency over time once it is applied. Additionally, the composition desirably should ensure that bioadhesion or tack is maintained despite the friction of the sexual act. Of course, such a composition desirably should not cause irritation to either the vaginal/cervical mucosa or the penile epithelium.

Because cervical mucus and fluid exuded from the vascular rich lamina propria of the vaginal epithelium can lead to relatively short contact times of active agents within topical contraceptive formulations[3], it is highly desirable to employ a bioadhesive formulation that enhances the adherence to the genital tissue to which it is applied (most preferably vaginal tissue). Such compositions have the added benefit of enhancing the contact time of the composition with sperm and leukocytes but also with vaginal and cervical epithelia. In the case of a topical contraceptive, although it is typically applied just prior to intercourse, its ability to remain in the vaginal vault for at least one to three days is advantageous over the long term especially since certain cannabinoids can have a high non-specific binding to the vaginal epithelium resulting in increased keratization and a mucoid cell layer overlying the stratified epithelium, which can, in turn, precipitate increased mucus production when administered intraperitoneally [4]. Additionally, the long lasting presence of the drug would have a continued effect on sperm motility over other spermatocides which usually last only a

few hours. Prolonged activity also would help the active agents within the composition prevent the sperm from undergoing an acrosomal reaction if any are able to reach the ovum.

While, for use in the inventive method, the 5'-alkyl resorcinol and/or cannabinoid compounds can be formulated in any appropriate and desired manner, the invention also provides a composition suitable for topical application to genital tissue that comprises at least one 5'-alkyl resorcinol and/or cannabinoid compounds and a water insoluble bioadhesive polymer as a hydrogel. Bioadhesive polymers are polymers that can adhere onto a biological substrate. Hydrogels are hydrophilic matrices capable of swelling and not dissolving in an aqueous media as water. The resorcinol and/or cannabinoid comound(s) can be loaded into these bioadhesive polymers, or hydrogels, so that as water is absorbed into the matrix, chain relaxation occurs and drug molecules are released through the spaces or channels within the hydrogel network [5].

Many bioadhesives are made of either synthetic or natural polymers. Most of the current synthetic bioadhesive polymers are either polyacrylic acid or cellulose derivatives. Representatives of polyacrylic acid-based polymers are carbopol, polycarbophil, polyacrylic acid (PAAc), polyacrylate, poly(methylvinylether-co-methacrylic) acid, poly(2-hydroxylethyl methacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), and poly(isobutylcyanoacrylate). Cellulosics include carboxymethyl cellulose, hydroxyethol cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, and methylhydroxyethyl cellulose. In addition, (semi) natural bioadhesive polymers include chitosan and various gums such as guar, xanthan, gellan, carrageenan, pectin, and alginate. Finally, PHPMAm, poly(vinylpyrrolidone), and poly(vinylalcohol) can be included as synthetic bioadhesive polymers [6]. To achieve the desired bioadherence and consitency, it is desirable for the polymer to constitute between about 0.5% and about 5% of the composition, more typically between about 1% and about 3% of the composition by weight.

A preferred polymer for use in this invention is Polycarbophil, U.S.P., which commercially available from B. F. Goodrich Speciality Polymers of Cleveland, Ohio under the trade name NOVEON® AA-1 USP. This water insoluble polymer has an apparent pKa of approximately 4.5, picks up 60-100 times its weight in water. It is a synthetic, non-absorbed, non-toxic, substance, which is stable to elevated temperatures and high oxygen content. Gels containing polycarbophil have been demonstrated to remain on vaginal tissue for 3-4 days and serve as a platform for the delivery of agents such as progesterone. Since the cannabinoids have been compared to the steroids in structure the use of polycarbophil as the principle functioning polymer is desirable.

Other bioadhesive polymers that can be used in conjunction with NOVEON® AA-1 are Noveon® Carbopol® 934P NF, Carbopol 974P NF, and Carbopol 971P NF. Carbopol 934P NF polymer has been used in oral suspensions and tablets worldwide since the mid 1960s. In the past ten years, Noveon, Inc. has designed two new products polymerized in

ethyl acetate, as toxicologically preferred alternatives to Carbopol 934P NF polymer. Carbopol 974P NF has similar rheological properties to Carbopol 934P NF: both are highly crosslinked polymers which produce semisolid formulations with very short flow rheology. Short flow rheology can be characterized as a gelled consistency similar to mayonnaise. Carbopol 971P NF is a lightly crosslinked polymer, which provides very low viscosities and excellent yield values at low usage levels. Semisolid dosage forms based on Carbopol 971P NF polymer have a longer rheology, and will flow in a manner not unlike honey [7]. Phase change polymers that undergo a change from liquid to semisolid also can be used. Examples of phase change polymers are poloxamer 407, sodium carboxymethycellulose, carbopol, hyaluronic acid, or xanthum gum.

Typically, bioadhesive polymers are fabricated by a polymeric reaction of a polymer or pre-polymer and a cross-linking agent. Suitable cross-linking agents include divinyl glycol, divinylbenzene, N,N-diallylacrylamide, 3,4dihydroxy-1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene and similar agents. The cross-linking agent desirably is present at such an amount as to provide enough bioadhesion to allow the system to remain attached to the target epithelial surfaces for a sufficient time to allow the desired dosing to take place. Also in most preferred practice, the bioadhesive contains about 0.05 % to about 2 % by weight cross-linking agent, although it may contain about 0.01 % to about 10 % by weight cross-linking agent. The polymer formulation can be adjusted to control the release rate of the drugs (cannabinoids and alkyl resorcinols) by varying the amount of cross-linking agent in the polymer. For example, greater than two percent of the cross-linking agent can decrease the ability of the polymer to absorb water and swell, which may be desirably in some systems.

The rheologic properties of a gel will determine the residence time of a given drug in the formulation which in contact with the desired surface. Its release will be determined by a number of factors including drug interaction with the polymer and the partition of the drugs to micelles [8]. The physical characteristics of the gels themselves are determined by the degree of cross-linking. For example, Carbomer 934P is a gel former that can be used in the inventive formulations, and which can be substituted by other gel formers, such as Carbomer 974P, Carbomer 980 and methyl cellulose or propyl cellulose. Although C981 and C940 differ in cross-linking density (C940 is more highly cross-linked), the release typically does not differ. Carbopol® 1342 which has a covalently bound, lipophilic modification, i.e., a long-chain (Cl0-C30) alkyl acrylate. It is belived to be the lipophilic interactions between the micelles and the polymer that results in the slower release from this gel. A slower release would be useful as a maintenance topical contraceptive providing a longer contact time with sperm. On the other hand, it has been shown that Carbomer 934P had a zero-order release in the small bowel of fasting rats.

For vaginal administration, preferably the formulation remains attached to the epithelial surfaces for a period of at least about twenty-four to about seventy-two hours. Such

results may be measured clinically over various periods of time. This preferred level of bioadhesion is usually attained when the cross-linking agent is present at about 0.1 to 6.0 weight percent of the polymer, with about 1.0 to 2.0 weight percent being most preferred, as long as the appropriate level of bioadhesion results. A convenient dosage form for vaginal self-administration is a gel. Thus, a product is prepared containing 1-3% polycarbophil plus the usual formulation of excipients to produce a thick emulsion-gel. The pH of the product can be adjusted to between 2.5 and 7, more typically between 3.0-6, depending upon its intended target treatment; typical pH for vaginal application is between about 4.5 and 6.5.

The interaction of the various Carbopols and polycarbophil can influence which combination of active agents and exipients is chosen. The higher calcium binding affinity found for Carbomer compared to, for example, polycarbophil can be ascribed to their different ways of cross-linking. Polycarbophil is cross-linked by divinylglycol and to a lower degree than carbomer, which is cross-linked by allylsucrose. For example, a study of the combination of polycarbophil and Carbopol 934P showed that the calcium binding affinity of polycarbophil was observerd to be statistically significant ($P < 0.05$) lower than for carbomer[9]. This higher calcium binding affinity found for a particular carbomer can have significance since calcium influx is involved in the acrosome reaction of the sperm [10]. It is, however, within the ordinary skill in the art to select an appropriate polymer and cross-linking agent suitable to the desired end-use.

The advantage that these materials possess is in their ability to provide retention of a drug at a mucosal surface for a period of time longer than that found for a simple liquid or powder system. Polymer blends such as polycarbophil and daichitosan can combine attributes of different polymers to give a superior bioadhesive [11]. Since the cannabinoids are highly lipophilic and have been shown to have high non-specific binding to the vaginal epithelium and less to the lamina propria [12], the inventive compositions can help prevent the drug and its vehicle from becoming adsorbed so that it remains available to act on sperm.

The use of dry dextran-starch microspheres is less preferred since it leads to a reversible shrinkage of the cells which ultimately leads to a physical separation of the intercellular junctions which would be undesirable in the setting of STDs, such as HIV-1, HSV-2 and bacterial pathogens.

Penetration enhancers (e.g., sodium glycocholate, sodium deoxycholate, and sodium lauryl sulfate), also can be incorporated into the inventive composition. Such agents can increase the permeability of the pharamaceutical agents across mucosa, and hence their bioavailability[13]. Where such penetration enhancers are included, typically they constitute between about 0.5 % to about 10 % w/v of the composition, and more typically between about 1 % and about 5 % w/v of the composition; however, somewhat more or less penetration enhancer can be employed as desired.

To prepare the cannabinoids or alkyl resorcinols for incorporation into the inventive formulation, the compounds can be dissolved or emulsified in a suitable carrier, typically an oil. Dissolving 1 gm of the drugs in 1 ml. alcohol or 10 gm of the drugs in 25 ml of warmed sesame oil has been the traditional route of solubilization [14]. However, hemp seed oil desirably is used instead of sesame oil in the inventive formulations. The preferred oils derived from hemp oil are polyunsaturated essential fatty acids: *gamma-* linolenic acid (c18:3w6) (GLA) and its metabolite (1-6%) dihomo-gamma-linolenic acid or DGLA (C20:3w6), LA linoleic acid (C18:2w6) (50-70%), LNA Linolenic (C18:3w3) (15-25%) which can have anti-oxidant effects. Other fatty acids can be used in the emulsifying complex: lipoic acid is both fat and water-soluble and is easily absorbed and transported across cell membranes and acts as both an extracellular and intracellular antioxidant. It forms an inclusion complex with β-cyclodextrin with a 1:1 stoichiometry. Coenzyme Q10 (ubiquinone) is another fatty acid with antioxidant effects and can be complexed with the cannabinoids and alkyl resorcinol(s). Although Tween 80 (polysorbate 80) has been used for emulsification in opthalmic preparations of cannabinoids, as an anionic detergent it is not preferred to be employed in the inventive compositions. Additionally, Tween 80 exhibits effects on uterus and oestrus cycle in the rat similar to DES[15]. Polysorbate can be replaced with 5% polyvinylpyrrolidone (PVP) which is also useful for its suspension capabilities as well as lubricating and adhesive properties. It can be complexed with povidone as a co-polymer. Those skilled in the art will know the methods by which an emulsion is prepared prior to solubilization. The hydrophile-lipophile balance or HLB will determine the specific ratios of emulsifying agents chosen for the admixture. For example, when sodium lauryl sulfate is used as an emulsifying agent it typically does not represent an amount greater than about 5% w/v to prevent any potential irritation to the vaginal mucosa. Sodium lauryl sulfate is more acid-stable and will maintain the emulsion in a pH range of 4.5 to 6.5 which is the ideal pH range of the vaginal secretions. Typically, where an emulsifying agent is included in the inventive composition, it represents between about 0.5 % to about 10 % of the composition, more typically between about 1 % and about 5 % of the composition, often about 3 % by weight of the composition.

In addition to the polymeric system, optional penetration agent, and optional emulsifying agent, the inventive compositions also can include a solubilizing agent. Preferred solubilizing agents are cyclodextrins (CDs), which are oligosaccharides having 6-8 glucopyranose units connected in a ring. Within the context of the present invention, the term "cyclodextrins" includes cyclodextrins and their derivatives, e.g., ether, ester and amide derivatives. Suitable cyclodextrins include alpha-cyclodextrin, beta-cyclodextrin and gamma-cyclodextrin, 2-hydroxy-propyl-β-cyclodextrin (2-HP β-CD), methyl-beta-cyclodextrin (2,6-DM14-β-CD), sulfobutylether β-cyclodextrin (SBE-β -CD), polymer-beta-cyclodextrin [16]. Their cyclic structure gives cyclodextrins a hydrophobic cavity.

Cyclodextrins typically are used to increase the water solubility of drugs by complexing them into the hydrophobic cavity of cyclodextrin [17]. Less polar drug molecules and hydrophobic drugs can enter these cavities, forming an inclusion complex. The inclusion complexation could enhance both the solubility and the stability of the included drug molecules. The distribution of the solutes between micelles can be influenced by cyclodextrins. Controlling the degree of substitution is important in balancing water solubility and complexing capability. For example, the introduction of a methyl substituent at the 2- and 6- positions appears to improve the inclusion of a variety of drugs to the CD cavity. Binding constants are on average 5 times greater for 2,6-DM 14-β-CD than for β -CD however due to the potential renal toxicity generally is not be used systemically (Thompson DO). Methyl groups seem to increase the hydrophobicity of the CD cavity as well as increase the solubility of the derivative over that of the parent CD. The extent of methylation is important in optimizing complexation. Two commercial preparations of (2HP)- β -CD, Encapsin and Molecusol®, recognized the need for this compromise and have substitution levels that provide a balance between solubility and complexation. Encapsin® and Molecusol® have MDS values of approximately 4 and 8, respectively.

Sulfobutylether β -CD: An optimal anionic CD. SBE-β -CD preparation exhibit good water solubilities and effective complexation characteristics at all levels ofsubstitution but a hepta-substituted preparation is the optimal specification for a commercial SBE β -CD derivative. This level of substitution effectively eliminates residual β -CD in the product most economically. SBE7-β -CD (Captisol) has high intrinsic aqueous solubility (> 50% wt/vol) and exhibits binding capacities comparable to unsubstituted β-CD but often better than HP-β-CD. Its inability to form 1:2 complexes may contribute to potential safety benefits. This is marketed as Captisol by Cydex. Captisol is not a penetration enhancer which is good for a membrane active drug.

There is a good correlation between sizes of cyclodextrin cavities and the cross-sectional area of the polymers which permit the delivery of the CD solubilized drug to reach the targeted tissue. Examples in the cannabinoid literature confirm the feasibility of solubilizing Δ^8-THC with a cyclodextrin: HE-211 solution was prepared at a 100 μM concentration in 10% β-hydroxypropyl cyclodextrin solution [18]. This may not translate into a molar ratio of 1:1. PCT application 99/32107 shows that β-hydroxypropyl cyclodextrin was used with THC. An inclusion complex comprising a β cyclodextrin, hydroxypropyl-β -cyclodextrin or SBE-β-CD in molar ratio of 1:1 or 1:2 with cannabinoid or alkyl resorcinol is desirable. A further embodiment comprises sufficient cyclodextrin to form an inclusion complex comprising gamma-cyclodextrin, hydroxypropyl-cyclodextrin and polymer-beta-cyclodextrin in molar ratio cannabinoid or alkyl resorcinol:cyclodextrin of 1:2 or 1:1. A still further embodiment comprises polymer-beta-cyclodextrin with molecular weight between 4000 and 4500 as the agent capable of forming an inclusion complex with the cannabinoid

and alkyl resorcinol. The weight ratio of solubilizing agent to cannabinoid is typically in the range of 100:1 to 5:1, preferably 30:1 to 10:1. Thus, where cyclodextrins are employed in the composition as solubilizing agents, they can represent between about 1% and about 25 % of the composition, more typically between about 3 % and about 20 % of the composition, such as between about 5 % and about 15 % of the composition.

Compositions useful in the present invention can also contain one or more pharmaceutically or cosmetically acceptable additives that are referred to herein as adjuvants that typically assist in providing extended shelf life and customer acceptance of a hygiene product. Exemplary adjuvants include preservatives, tissue toners, tissue conditioning agents, tissue feel enhancers, emollients, lubricating oils (e.g., lipids), emulsifying agents, humectants, coloring agents, and odor providing agents (odorants).

Typical preservatives known for use with feminine hygiene products include alcohol, ascorbyl palmitate, benzoic acid, butylated hydroxyanisole, butylated, hydroxytoluene, chlorobutanol, ethylenediamine, ethylparaben, ethyl vanillin, glycerin, methylparaben, monothioglycerol, phenol, phenylethyl alcohol, phenylmercuric nitrate, propylparaben, sassafras oil, sodium benzoate, sodium formaldehyde sulfoxylate, sodium metabisulfite,sorbic acid, sulfur dioxide, maleic acid, and propyl gallate. Obviously, to the extent any of the foregoing preservatives are irritating to the vagina, less irritating preservatives can be chosen.

Typical emollients known for use with feminine hygiene products, which are useful herein, are generally bland, fatty or oleaginous substances including castor oil, sulfated castor oil, cocoa butter, coconut oil, cold cream, corn oil, cotton-seed ail, rosewater ointment (also known as cold cream), combinations of sodium lauryl sulfate, propylene glycol and stairwell alcohol, sesame oil, theobroma oil, myristyl alcohol and shark liver oil.

Typical lubricating agents or oils known for use with feminine hygiene products, which are useful herein, are petrolatum, white or yellow wax, coca butter, oleic acid, olive oil, jojoba oil, paraffin, starch glycerite, lanolin, hydrophilic petrolatum, mineral oil, acetyl alcohol, glyceryl monostearate, stearic acid, polyethylene glycols, polyoxyl 40 stearate, polysorbate, silicone elastomer, cbolesterol and higher molecular weight lipids. Where present, typically such lubricating agents constitute between about 0.5 % and about 5 % of the composition by weight, such as between about 1 % and about 3 % of the composition

Emollients and lubricants provide hygiene products with the appropriate slip, tactile feel and rub-in properties to enhance the ease of usage and to encourage the consumer to use the product more liberally and more frequently. Certain quaternary compounds allow substances like petrolatum be combined with glycerine and in personal-care products without feeling greasy. The petrolatum-glycerine combinations especially effective in alleviating dry skin. Typical emulsifying agents known for use with feminine an hygiene products, which are useful herein, are sodium alginate, carbomer, sodium carboxymethylcellulose, carrageenan,

gelatin, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, octoxynol-9, oleyl alcohol, polyvinyl alcohol, povidone, sodium lauryl sulfate, sorbitan esters, stairwell alcohol, tragacanth, and xanthan gum. Emulsifying agents are used to produce oil-in-water emulsions and can be classified into three types: monomolecular, multimolecular and solid particle. Known monomolecular emulsifying agents include potassium laurate, polyoxyethylene sorbitan monooleate. Multimolecular emulsifying agents include acacia and gelatin. Solid particle emulsifying agents include bentonite, graphite and magnesium hydroxide. Emulsifying agents can also be classified chemically into anionic, cationic and nonionic.

Typical humectants known for use with feminine hygiene product agents, which are useful herein, are glycerin, propylene glycol, pyrrolidone carboxylic acid, sodium lactate, urea, and certain natural lipid mixtures. Other known humectants include certain proteins, gelatin, hyaluronic acid, vitamins and some natural ingredients. Some of the proteins used are collagen, elastin, placental proteins and proteins from epidermal tissues of mammals are also used.

The composition also can contain one or more preservatives, such as are commonly-employed in the art. A preferred preservative is methyl- and propylparabens and sorbic acid[19], but others can be used as desired.

One combination of the above compounds –polycarbophil, Carbopols, cyclodextrins, 5% polyvinylpyrrolidone with the combined emulsion admixture of the novel cannabinoids and/or resorcinol with lipoic acid and Coenzyme Q10 as an emulsion – can produce a suitable composition for use in the inventive method. The exact formulation can vary depending on the delivery mode, i.e. gel, suppository, gelatin capsule or slow delivery device. However, in general, the ranges of the excipients on a weight percent basis (unless as otherwise noted) can be as follows:

Solvent	Purified water:40 to 80%
Emulsifying agents	Polyvinylprrilone with povidone: 1 to 5% Lipoic acid or Coenzyme Q 10 or linoleic or gamma-linoleic acid or hemp oil: 1 to 3%
Active Agent	Cannabinoid or alkyl resorcinol: 1 to 10% (to provide from 10 to 100 μM/ml)
Solubilizing agents	cyclodextrins: 5 to 15%

Bioadhesives:	NOVEON® AA-1 (polycarbophil) (1 to 3%) Carbopol (a gel forming polymer) (1 to 3%) Chitosan
Permeability enhancers	Sodium glycocholate (1 to 5% w/v) Sodium lauryl sulfate (1 to 5% w/v)
Preservatives	Methylparaben (0.5 to 2%)
Lubricating agents	Propylene glycol or Silicone elastomer, Dow Corning (1 to 3%)

In use, the composition is applied in an amount of about 0.01 to about 5 mg/cm^2 , such as between about 0.05 and about 3 mg/cm^2 and of contacted vagina cells. Given that the vagina has, on average, an interior surface area of about 40 cm^2, a dosage of about 1.75 grams to 2.5 grams of the inventive composition can be employed. However, more or less of the composition can be used as desired. In fact, application to the vaginal epitheliums can be and preferably is excess of that needed to provide contraception and, in some applications, microbicidal activity.

In order to deliver the product of the inventive method to the vagina and cervix, and suitable method can be employed, e.g., by a cervical cap or diaphragm containing a gel, by insertion of a suppository or gel cap administered by a plunger, as a gel or solution administered by a catheter attached to a container, vaginal sponge, disposable squeeze bottle or needleless syringe, or by a douche or other suitable instrument such as a fenestrated tampon like device or contained in a male condom. Any of the devices which are introduced into the vagina for the delivery of the compositions can be coated by a material which will promote the release of the composition from the internal storage chamber. Alternatively, the inventive product can be delivered by a soft elastic capsule, which can dissolve in the vaginal environment. The gelation can be further plasticized by the addition of glycerin, sorbitol, or a similar polyol. Of a major concern is the source of the gelatin. If it is animal source, religious concerns may prevent its use particularly in Hindu and Muslim countries, unless it were derived from fish. Kosher preparations are available and synthetic, animal free gel caps may become available.

Testing of topical contraceptives can be achieved by *in vitro* screening methods incorporating human sperm with the drug candidate and utilizing immobility or loss of functionality as an end-point [20]. Although conventional visual observation tests, such as the Sander-Cramer method [21] are used as a preliminary screening assay for candidate topical contraceptives, the numerous *in vivo* factors such as distribution of the spermicide in the

vagina, removal or displacement of the spermicide by the coital act, and effects of vaginal fluids on the spermicide which affect the agent require more sophisticated testing modalities. Many of these tests were developed to determine the many causes of male infertility and measure sperm quantity, motility and morphology.

The Contraceptive Research and Development (CONRAD) Program established a special project, the Spermicidal Testing Program (STP), to evaluate new putative spermicide, as well as to create and validate screening methodology [22]. There appears to be no explicit testing algorithm for chemical vaginal contraceptive (CVC) candidates in the contraceptive literature; therefore, a tentative flow chart far preclinical evaluation is presented (Fig. 1).

The particular path in the algorithm which is taken will depend on the concentration of the test compound to achieve the immobilization as determined by the initial screening test, a modified Sander-Cramer Assay which uses serial two-fold dilutions of the compound in saline and normal semen samples. Its end point is total sperm immobilization in a 20-second incubation. Six to 10 different semen samples arc used to achieve more reliable results, usually expressed as compound minimum effective concentration (MEC). The MEC for a given agent is obtained using the highest dilution, from the serial dilution set, which displays spermicidal activity. A compound that presents a MEC <2.0 mg/ml in the modified Sander-Cramer assay has a significant sperm immobilizing activity and can be considered as a spermicidal agent. The MEC limit stated above is arbitrary and represents around 10 to 20 times the MEC of the standard positive control nonoxynol-9 (N-9) preparation (Ortho-OW48).

Cervical mucus penetration (CMP) assays have been extensively used in infertility diagnosis and can be applied for contraceptive evaluation since an important characteristic of a test agent is the capacity to "biodiffuse" in cervical mucous (CM) that is to diffuse in CM while keeping its biological activity. Again, these tests have been modified by CONRAD use a CMP assay variant called Double-End Test (DET), which is the next step in our testing flow once a compound has been determined to have a MEC <2.0 mg/ml. Briefly, the DET consists of an incubation in a test agent solution of bovine CM tubes (Penetrak ®, Serono-Baker) opened at one end, followed by another incubation of the same tube opened al the other end in a semen sample. In this way, spermatozoa migrate in an opposite direction to that of the compound, eventually ceasing their penetration where they find a compound bioactive concentration. Thus, penetration of vanguard motile sperm is recorded and compared to that of the control, i.e., the solvent. Results are expressed as percent of control sperm penetration and are inversely correlated with compound biodiffusion. Despite the controversy about the significance of the distance traveled by vanguard motile sperm we chose this endpoint for it is operationally convenient in the initial CVC screening.

The uninterrupted coating of vaginal epithelium by a CVC is thought to play a role in the prevention of STD and HIV. For this reason bioadhesion will be evaluated not only for the test compound but also for the contraceptive formulation.

By and large, the rabbit vaginal irritation model has been widely used [23]. Briefly, the test CVC is instilled into the vagina of approximately five rabbits per group, once daily for 10 days. Doses may vary, but typically are be in relation to the proposed human dose. Additional rabbits are included as sham and untreated controls. The animals are sacrificed on the day following the last treatment (11th day) and the vaginas removed, macroscopically examined and processed for histopathological evaluation. If the compound's performance justifies further testing, then an *in vivo* model using the stumptailed macaques will be used [24].

On the right side of the CVC screening algorithm, after the test compound proves not to have a high spermicidal activity in the modified Sander-Cramer assay, i.e., MEC >2.0 mg/mL, several assays can be performed to assess its contraceptive potential (Fig. 1).

A sperm viability test after a short incubation with the test compound could be the next step in the evaluation. Dead spermatozoa are no longer able to maintain a selective permeability at their plasma membrane. Therefore, electrochemically charged stains like Eosin Y can penetrate and distinctly label such cells. This type of test helps to determine whether the agent has any spermicidal activity at concentrations lower than 0.2 percent and under different experimental conditions.

Subsequently, a set of CMP assays enable the investigation of sperm migration blocking effects. The first assay, called "modified One- End Test" (mOET) consists of a 30 minute incubation of bovine CM tubes in the compound solution, followed by another incubation (60 minutes) of the same tubes after mixing a semen sample with the compound. The end point is penetration length of motile vanguard sperm. If sperm penetration is similar to that of the control, the agent does not have blocking activity. Conversely, if sperm migration is impeded, the compound could be active on either the CM or some sperm motion parameters. In this latter case, a "simultaneous One-End Test" (sOET), consisting of a very short compound- sperm pre-incubation and the subsequent immersion of CM tubes in that mixture, could be helpful. If positive, i.e., abnormal penetration with the test compound, emphasis may be placed on a sperm alteration.

Computer-assisted semen analysis (CASA) is a relatively new and invaluable aid to verify this hypothesis. Determination of percent of motile cells, velocity (VEL), linearity (LIN), amplitude of lateral head displacement (ALH), flagellar beat/cross frequency (B/C freq.), and other sperm motion parameter can pinpoint compound actions that otherwise would pass inadvertently. Correlation between several of these parameters and sperm penetration in CM has been clearly demonstrated.

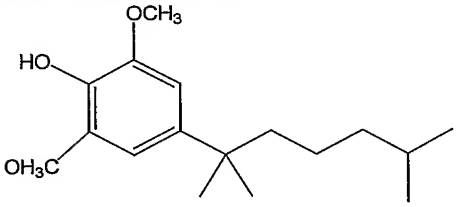
Sperm capacitation and acrosome reaction, as well as binding and penetration of zona pellucida and oolemma, are key events in human fertilization. Blockage of any of these

processes by a CVC candidate would result in contraceptive activity. Protocols for identification of acrosomal status, hamster-egg penetration test and zona binding/penetration assays can be modified to assess anti-fertility effects.

Since incubation of semen with spermicidal agents showed a temporal activity pattern, exposure time to a vaginal contraceptive is a factor which is crucial to its successful use. The duration of exposure of sperm to spermicidal agent can follow the protocol established by WHO [25]. Upon detection of contraceptive activity in the test compound, anti-STD as well as mucosal adhesion and irritation studies can be carried out.

PREPARATORY EXAMPLE 1

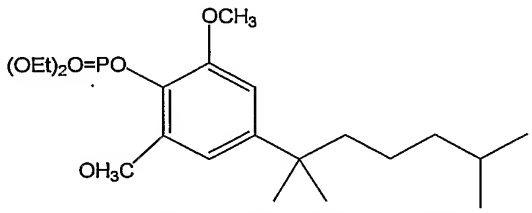
A mixture of 2,6-dimethoxyphenol (73.4 g, 0.48 mole), 2,6-dimethyl-2-heptanol (69.0 g, 0.48 mole) and methanesulfonic acid (95 mL) was stirred at 50 °C for 3 h and then at room temperature overnight. The mixture was poured over ice-water (600 mL) with stirring. The mixture was extracted with CH_2Cl_2 (2 x 200 mL). The extracts were washed with water, saturated aqueous $NaHCO_3$, saturated aqueous sodium chloride solution and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to obtain the product as an oil (130 g, 96%). Analysis of this substance (MS (FAB) m/z 281 (MH)+; 1H NMR (CDCl3) δ 0.80 (d, 6H), 1.0-1.1 (m, 4H), 1.27 (s, 6H), 1.40-1.60 (m, 3H), 3.89 (s, 6H), 5.36 (s, 1H), 6.54 (s, 2H)) revealed it to be 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenol (referred to hereinafter as IMG-502):



PREPARATORY EXAMPLE 2

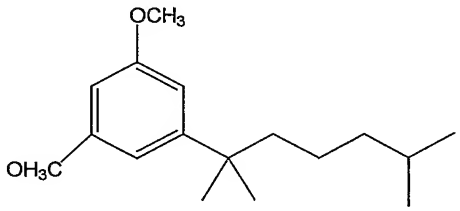
A solution of crude 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenol from Example 1 (130 g, 0.46 mole) in dry CCl_4 (100 mL) was cooled in ice-bath and diethyl phosphite (70 mL, 0.54 mole) was added. To the stirred mixture triethylamine (75 mL, 0.54 mole) was added dropwise at such a rate as to maintain the temperature of the reaction mixture below 10 °C. The reaction mixture was stirred in the ice-bath for 2 h and at room temperature overnight. The mixture was then diluted with CH2Cl2 (200 mL), washed with water, 4N aqueous NaOH (100 mL), 1N aqueous HCl (125 mL), water and saturated aqueous sodium chloride solution. The extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography over a column of silica using cyclohexane:EtOAc (7:1 to 3:1 gradient) as the eluent to obtain 103 g (54%) of the product as a colorless waxy oil. Analysis of this substance (MS (FAB) m/z 417 (MH)+. 1H NMR (CDCl3) δ 0.81 (d, 6H), 1.0-1.1 (m, 4H), 1.26 (s,

6H), 1.35-1.6 (m, 9H), 3.86 (s, 6H), 4.25-4.38 (m, 4H), 6.53 (s, 2H)) revealed it to be 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenyl diethyl phosphate:



PREPARATORY EXAMPLE 3

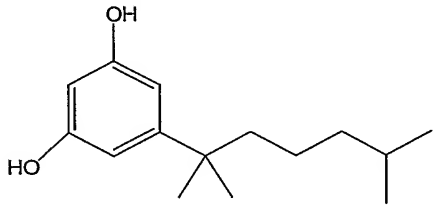
A solution of 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenyl diethyl phosphate from Example 2 (82 g, 0.197 mole) in Et_2O (175 mL) and THF (35 mL) was added slowly to liquid ammonia (450 mL) contained in a 3-neck vessel fitted with mechanical stirrer, thermometer, dry ice condenser and a pressure equalizing addition funnel while adding small freshly cut pieces of lithium wire (2.8 g, 0.40 g-atom) at such a rate as to maintain a blue color. The reaction mixture was stirred further for an hour and then quenched by the addition of saturated aqueous NH_4Cl (22 mL). Ether (220 mL) was added and the ammonia was allowed to evaporate overnight. The residue was treated with water (220 mL). The layers were separated and the ether layer was washed with 4N NaOH (200 mL), water (2 x 200 mL) and saturated aqueous sodium chloride solution. The organic extracts were dried (MgSO4) and concentrated under reduced pressure. The crude product was purified by chromatography over a column of silica using cyclohexane:EtOAc (95:5) as the eluent to obtain 43 g (83%) of the product as a colorless oil. Analysis of this substance (MS (FAB) m/z 265 (MH)+; 1H NMR (CDCl3) δ 0.80 (d, 6H), 1.00-1.10 (m, 4H), 1.26 (s, 6H), 1.4-1.6 (m, 3H), 3.79 (s, 6H), 6.30 (m, 1H), 6.49 (m, 2H)) revealed it to be 4-(1,1,5-trimethylhexyl)-2,6-dimethoxybenzene (referred to hereinafter as IMG-503):



PREPARATORY EXAMPLE 4

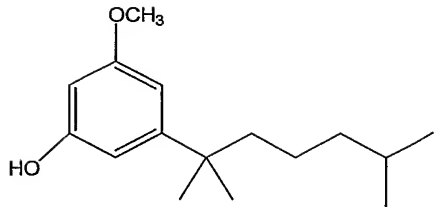
A solution of 4-(1,1,5-trimethylhexyl)-2,6-dimethoxybenzene from Example 3 (10 g, 0.038 mole) in anhydrous CH_2Cl_2 (100 mL) was cooled in ice-bath and was treated dropwise with a solution of boron tribromide in CH_2Cl_2 (100 mL of 1M solution, 0.10 mole) over a period of 1 h. The mixture was stirred in the cold bath for 2 h and then at room temperature overnight. The reaction mixture was cooled in ice-bath and cautiously

treated with water (100 mL). The resulting mixture was diluted with CH_2Cl_2 (100 mL) and treated with half-saturated aqueous sodium bicarbonate solution. The layers were separated, the organic layer was concentrated to half volume under reduced pressure and extracted with 2N aqueous NaOH (2 x 75 mL). The aqueous alkaline extract was cooled and acidified to pH 3.0 with 1N aqueous HCl. The acidified mixture was extracted with Et_2O (2 x 100 mL). The ether layer was washed with saturated aqueous sodium chloride solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product thus obtained was purified by chromatography over a column of silica using cyclohexane:EtOAc (8:1 to 4:1 gradient) as the eluent to obtain 8.0 g (90%) of the product as colorless crystalline solid. Analysis of this substance (Mp 95-96 °C. MS (FAB) m/z 237 (MH)+; 1H NMR (CDCl3) δ 0.80 (d, 6H), 1.00-1.10 (m, 4H), 1.23 (s, 6H), 1.40-1.58 (m, 3H), 4.65 (s, 2H), 6.17 (m, 1H), 6.38 (m, 2H)) revealed it to be 5-(1,1,5-trimethylhexyl) resorcinol (referred to hereinafter as IMG-501):



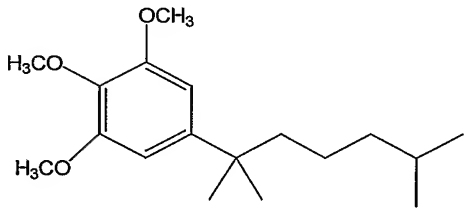
PREPARATORY EXAMPLE 5

A solution of 4-(1,1,5-trimethylhexyl) resorcinol from Example 4 (2 g, 0.0076 mole) in anhydrous CH_2Cl_2 (10 mL) was cooled in ice-bath and was treated dropwise with a solution of boron tribromide in CH_2Cl_2 (2.6 mL of 1M solution, 0.0026 mole). The mixture was stirred in the cold bath for 2 h and then at room temperature overnight. The mixture was cooled in ice-bath and cautiously treated with water (10 mL) followed by saturated aqueous sodium bicarbonate (5 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography over a column of silica using cyclohexane:EtOAc (8:1 to 4:1 gradient) as the eluent to obtain 0.364 g (19%) of the product as a colorless oil. Analysis of this substance (MS (FAB) m/z 251 (MH)+; 1H NMR (CDCl3) δ 0.80 (d, 6H), 1.00-1.10 (m, 4H), 1.24 (s, 6H), 1.4-1.6 (m, 3H), 3.78 (s, 3H), 4.67 (s, 1H), 6.23 (m, 1H), 6.40 (m, 1H), 6.47 (m, 1H)) revealed it to be 3-methoxy-5-(1,1,5-trimethylhexyl)phenol (referred to hereinafter as IMG-504):



PREPARATORY EXAMPLE 6

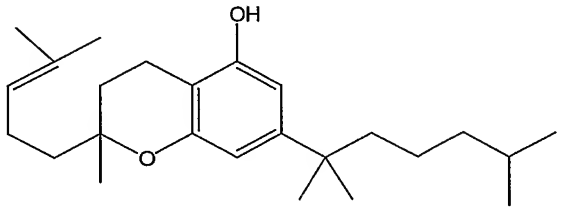
To solution of crude 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenol from Example 1 (0.19 g, 0.68 mmol) in dry THF (6 mL) was added iodomethane (0.78 g, 5.4 mmol). The mixture was treated with 60% dispersion of sodium hydride in mineral oil (0.06 g, 1.5 mmol) under nitrogen atmosphere. The mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The residue was treated with ether (20 mL). Water (5 mL) was added cautiously. The layers were separated, the ether layer was washed with water (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography over a column of sillica using cyclohexane/EtOAc 6:1 as the eluent to obtain 0.17 g (85%) of the product. Analysis of this substance (MS (FAB) m/z 295 (MH)+. 1H NMR (CDCl3) δ 0.81 (d, 6H), 1.0-1.2 (m, 4H), 1.28 (s, 6H), 1.40-1.60 (m, 3H), 3.84 (s, 3H), 3.87 (s, 6H), 6.53 (s, 2H)) revealed it to be 1-(1,1,5-Trimethylhexyl)-3,4,5-trimethoxybenzene (referred to hereinafter as IMG-507):



PREPARATORY EXAMPLE 7

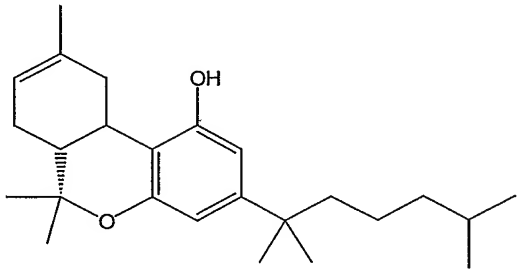
A solution of 1-(1,1,5-Trimethylhexyl)-3,4,5-trimethoxybenzene from Example 6 (0.344 g, 1.5 mmol) and geraniol (0.348 g, 1.5 mmol) and p-toluenesulfonic acid (0.03 g) in dry benzene (50 mL) was heated at reflux for 2 h. The mixture was concentrated to dryness. The crude product was purified by chromatography over preparative thick layer plates (2 x 0.25 mm) using cyclohexane:EtOAc 5:1 as the developing solvent followed by chromatography over a column of silica using cylcohexane/EtOAc 95:5 as the eluent to obtain 0.107 g (20%) of the product. Analysis of the compound (MS (FAB) m/z 373 (MH)+. 1H NMR (CDCl3) δ 0.80 (d, 6H), 1.0-1.2 (m, 4H), 1.21 (s, 6H), 1.31 (s, 3H), 1.4-1.51 (m, 2H), 1.52-1.7 (m, 9H), 1.7-1.9 (m, 2H), 2.0-2.15 (m, 2H), 2.60 (t, 2H), 4.56 (s, 1H), 5.1 (m, 1H), 6.31 (s, 1H), 6.39 (s, 1H)) revealed it to be 3,4-Dihydro-2-methyl-2-

(4-methyl-3-pentenyl)-7-(1,1,5-trimethylhexyl)-2H-1-benzopyran-5-ol (referred to hereinafter as IMG-508):



PREPARATORY EXAMPLE 8

A solution of 5-(1,1,5-trimethylhexyl) resorcinol (0.472 g, 2 mmol), p-menth-2-ene-1,8-diol (0.30 g, 2.1 mmol) and p-toluenesulfonic acid (0.084 g) in dry benzene (25 mL) was refluxed under a Dean-Stark trap for 4 h. The mixture was cooled to room temperature and treated with saturated aqueous sodium bicarbonate (25 mL). The layers were separated. The aqueous layer was extracted with benzene. The combined organic extracts were dried (MgSO4) and concentrated under reduced pressure. The crude product was chromatographed over a column of silica gel using cyclohexane/EtOAc 95:5 as the eluent to obtain 0.22 g (30%) of the product. Analysis of the product (MS (FAB) m/z 371 (MH)+. 1H NMR (CDCl3) δ 0.80 (d, 6H), 1.00-1.10 (m, 4H), 1.11 (s, 3H), 1.21 (s, 6H), 1.39 (s, 3H), 1.4-1.52 (m, 3H), 1.71 (s, 3H), 1.75-1.95 (m, 3H), 2.1-2.2 (m, 1H), 2.62-2.73 (m, 1H), 3.12-3.25 (m, 1H), 4.61 (s, 1H), 5.4-5.5 (m, 1H), 6.23 (s, 1H), 6.39 (s, 1H)) revealed it to be 3-Norpentyl-3-(1,1,5-trimethylhexyl)-Δ8-tetrahydrocannabinol (referred to hereinafter as IMG-509):



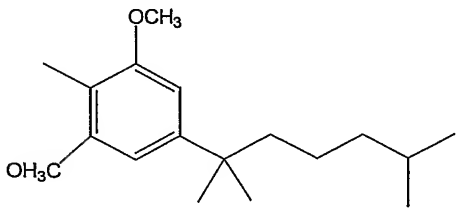
PREPARATORY EXAMPLE 9

A solution of 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenol (10 g, 35.7 mmol) in dry pyridine (70 mL) was cooled to 0 °C. To the stirred solution was added dropwise trifluoromethanesulfonic anhydride (11 g, 39 mmol). After the addition was complete, the reaction mixture was allowed to warm to room temperature and stir at room temperature overnight under argon. To the mixture was added an additional quantity of trifluromethanesulfonic anhydride (1.7 g, 6 mmol) and stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure to remove most of the pyridine. The residue was treated with cold water (100 mL) and extracted with

CH_2Cl_2 (3 x 50 mL). The organic extracts were washed with 1N HCl and brine, dried and concentrated under reduced pressure to obtain an orange syrup (14 g, 95%). The triflate thus obtained was used as such in the next step.

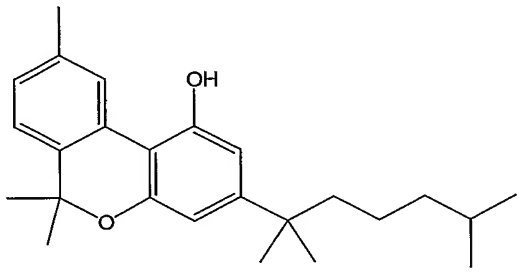
A mixture of the above triflate (10 g, 23.3 mmol), anhydrous lithium chloride (8.3 g, 196 mmol), triphenylphosphine (3.83 g, 14.6 mmol) and dichlorobis(triphenylphosphine)palladium (II) (1.8 g, 2.6 mmol) in anhydrous DMF (110 mL) was placed in a stainless steel pressure vessel under an atmosphere of nitrogen. To this mixture was added tetramethyltin (10 g, 56 mmol) and a few mg of 2,6-di-tert-butyl-4-methylphenol. The mixture was heated in an oil bath at 120 °C for 24 h. An additional quantity of tetramethyltin (5.5 g, 19 mmol) and a few crystals of 2,6-di-tert-butyl-4-methylphenol were added and the mixture was heated at 130 °C for 24 h. The mixture was cooled to room temperature and was filtered through a pad of celite to remove the palladium catalyst. The filtrate was concentrated under reduced pressure to ¼ the volume and filtered to remove yellow solid. The filtrate was further concentrated to near dryness. The residue was dissolved in CH_2Cl_2 (200 mL) and washed successively with 1.5 N HCl (5 x 100 mL), saturated aqueous potassium fluoride (5 x 50 mL), and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to obtain dark oil. This was purified by chromatography over a column of silica using cyclohexane/CH_2Cl_2 gradient (97:3 to 90:10) to obtain 1.82 g (27%) of the dimethoxy methyl compound. This product was utilized as such in the next step.

A solution of the above dimethoxy compound (1 g, 3.6 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and treated dropwise with 1M solution of BBr3 in CH_2Cl_2 (7.2 mL, 7.2 mmol). The mixture was stirred in the cold bath for 2 h and then at room temperature overnight. The reaction mixture was cooled in an ice bath and diluted with half-saturated aqueous sodium bicarbonate solution (20 mL). The mixture was diluted with CH_2Cl_2 (25 mL), and the layers were separated. The organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to obtain a beige solid which was purified by chromatography over a column of silica using cyclohexane/EtOAc 95:5 as the eluent to obtain 0.41 g (46%) of the product. Analysis of the product (Mp 145-147 °C. MS (FAB) m/z 251 (MH)+. 1H NMR (CDCl3) d 0.80 (d, 6H), 1.00-1.10 (m, 4H), 1.21 (s, 6H), 1.40-1.55 (m, 3H), 2.11 (s, 3H), 2.07 (s, 2H), 6.37 (s, 2H)) revealed it to be 2-Methyl-5-(1,1,5-trimethylhexyl)resorcinol (referred to hereinafter as IMG-510):



PREPARATORY EXAMPLE 10

A mixture of 3-norpentyl-3-(1,1,5-trimethylhexyl)-Δ8-tetrahydrocannabinol (1.4 g, 3.8 mmol) and elemental sulfur (0.3g, 0.5 mmol) was placed in a test tube and heated in a sand bath at 240-260 °C for 3 h. The crude product was purified by chromatography over a column of silica using cyclohexane/EtOAc 97:3 as the eluent to obtain 0.7 g (51%) of the product. Analysis of the product (MS (FAB) m/z 367 (MH)+. 1H NMR (CDCl3) δ 0.79 (d, 6H), 1.00-1.11 (m, 4H), 1.25 (s, 6H), 1.38-1.58 (m, 3H), 1.60 (s, 6H), 2.39 (s, 3H), 5.09 (s, 1H), 6.41 (s, 1H), 6.56 (s, 1H), 7.05 (d, 1H), 7.15 (d, 1H), 8.16 (s, 1H)) revealed it to be 3-Norpentyl-3-(1,1,5-trimethylhexyl)cannabinol (referred to hereinafter as IMG-511):



EXPERIMENTAL EXAMPLE

Test compounds IMG-510 and IMG-511 were dissolved in DMSO (10 mg/ml) and tested using a Sander-Cramer Assay for effect on sperm motility. A solution of nonoxynon-9 was employed as a control. The results are presented in Table 1. From these data, it can be concluded that IMG-510 displayed sperm-immobilizing activity against human sperm under the conditions of the Sander-Cramer assay above that of the solvent control (DMSO). Conversely, IMG-511 did not demonstrate spermicidal activity above the control.

COMPOUND CODE	SOLVENT	INITIAL CONC (mg/ml)	HIGHEST SPERMICIDAL DILUTION (1/X)	M.E.C. (mg/ml)	n	SOLUBILITY
IMG-510	DMSO	10	14.4±4.2	0.938±0.177	5	OK
IMG-511	DMSO	10	2.4±0.4	4.5±0.4	5	OK - clear yellow
Nonoxynol-9	DMSO	10	70.4±14.0	0.172±0.034	5	OK
DMSO			3.2±0.4	N.A.	5	OK

INCORPORATION BY REFERENCE

All sources (e.g., inventor's certificates, patent applications, patents, printed publications, repository accessions or records, utility models, world-wide web pages, and the like) referred to or cited anywhere in this document are hereby incorporated into and made part of this specification by such reference thereto, including, but not limited to, the following cited references:

1. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ. 2001 Jul 21;323(7305):131-4.
2. Kemmeren JM, Tanis BC, van den Bosch MA, Bollen EL, Helmerhorst FM, van der Graaf Y, Rosendaal FR, Algra A. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. Stroke. 2002 May;33(5):1202-8.
3. Robinson JR, Bologna WJ Vaginal and reproductive system treatments using a bioadhesive polymer Journal of Controlled Release, 28 (1994) 87-94.
4. Solomon J, Cocchia MA, DiMartino R. Effect of delta-9-tetrahydrocannabinol on uterine and vaginal cytology of ovariectomized rats. Science. 1977 Mar 4;195(4281):875-7.
5. Shojaei AH Buccal Mucosa As A Route For Systemic Drug Delivery: A Review J Pharm Pharmaceut Sci 1998 1(1):15-30
6. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: the next generation. J Pharm Sci. 2000 Jul;89(7):850-66. Review.
7. Noveon Technical Bulletin 16, B.F. Goodrich Co., Cleveland, OH
8. Paulsson M; Edsman K Controlled drug release from gels using surfactant Pharmaceutical research. 2001 Nov;18(11):1586-92
9. Luessen HL, Verhoef JC, Borchard G, Lehr CM, de Boer AG, Junginger HE. Mucoadhesive polymers in peroral peptide drug delivery. II. Carbomer and polycarbophil are potent inhibitors of the intestinal proteolytic enzyme trypsin. Pharm Res. 1995 Sep;12(9):1293-8.
10. Schaefer M, Hofmann T, Schultz G, Gudermann T. A new prostaglandin E receptor mediates calcium influx and acrosome reaction in human spermatozoa. Proc Natl Acad Sci U S A. 1998 Mar 17;95(6):3008-13.
11. Lehr CM, Bouwstra Ja, Schacht EH, Junginger HE. 1992. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm 78:43-48.
12. Lynn AB, Herkenham M. Localization of cannabinoid receptors and nonsaturable high-density cannabinoid binding sites in peripheral tissues of the rat: implications for receptor-mediated immune modulation by cannabinoids. J Pharmacol Exp Ther. 1994 Mar;268(3):1612-23.

13. Gandhi, R. and Robinson, J., Mechanisms of penetration enhancement for transbuccal delivery of salicylic acid, Int. J. Pharm.1992, 85:129-140.
14. Rosenkrantz H, Thompson GR, Braude MC. Oral and parenteral formulations of marijuana constituents. J Pharm Sci. 1972 Jul;61(7):1106-12.
15. Gajdova M, Jakubovsky J, Valky J. Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats. Food Chem Toxicol. 1993 Mar;31(3):183-90.
16. Thompson DO Cyclodextrins - Enabling Excipients: Their Present and Future Use in Pharmaceuticals, Critical Reviews In Therapeutic Drug Carrier Systems, 14(1):1-104.
17. Sutinen R; Kekki M;Paronen P Effect of cyclodextrin on the drug release from pH-controlled Silicone microspheres 261-264.
18. Eshhar N, Striem S, Kohen R, Tirosh O, Biegon A. Neuroprotective and antioxidant activities of HE-211, a novel NMDA receptor antagonist. Eur J Pharmacol. 1995 Sep 5;283(1-3):19-29.
19. Remington's The Science and Practice of Pharmacy, 20th ed., Lippincott Williams and Wilkins, Philadelphia, PA. (2000), p. 889
20. Lee CH. Review: in vitro spermicidal tests. Contraception. 1996 Sep;54(3):131-47. Review.
21. Sander EV, Cramer SD. A practical method for testing the spermicidal action of chemical contraceptives. Human Fertil 1941;6:134.
22. Barrier Contraceptives: Current Status and Future Prospects. Proceedings of the Fourth Contraceptive Research and Development Program International Workshop, Santo Domingo, Dominican Republic, March 22-25,1993 Ed. Mack CF, Darter M, Gabelnick HL, Spieler JM, Rivera R. Chapter 10: Chemical Vaginal Contraceptives: Preclinical Evaluation, 147-162.
23. Hahn DW (1980): Preclinical evaluation of new vaginal contraceptives. In Zatuchni GI, Sobrero AJ, Speidel JJ (eds): "Vaginal Contraception: New Developments". Hagerstown: Harper & Row, pp 234-246
24. Zaneveld LJ, Burns JW, Goodpasture JC, Vickery BH. Evaluation of the in vivo efficacy of a new vaginal contraceptive agent in stumptailed macaques. Fertil Steril. 1984 Mar;41(3):455-9.
25. World Health Organization. WHO laboratory manual or the examination of human semen and semen-cervical mucus interaction. 3rd ed. Cambridge: The Press Syndicate of the University of Cambridge, 1992.

WHAT IS CLAIMED IS:

1. A method of contraception comprising applying a composition comprising at least one 5'-alkyl resorcinol and/or cannabinoid compound to an individual in an amount and at a location sufficient to prevent pregnancy.

2. The method of claim 1, wherein the compound is a cannabinoid selected from the group consisting of cannabinol derivatives, Δ8-THC derivatives, cannabichromene derivatives, cannabidiol derivatives, cannabigerol derivatives

3. The method of claim 1, wherein at least one compound is IMG507, IMG508, IMG509, IMG510, or IMG511.

4. The method of claim 1, wherein the composition is applied to genital tissue.

5. The method of claim 1, wherein the composition comprises a barrier contraceptive device.

6. The method of claim 5, wherein the barrier contraceptive device is a condom.

7. The method of claim1, wherein the composition is a gel, cream, salve, or other fluid or semi-fluid formulation.

8. The method of any of claims 1-7, wherein the compound is present in the composition in an amount of from about 1 μM/ml to about 1000 μM/ml.

9. The method of any of claims 1-7, wherein the compound is present in the composition in an amount of from about 10 μM/ml to about 100 μM/ml.

10. The method of any of claims 1-7, wherein the compound is present in the composition in an amount of from about 25 μM/ml to about 75 μM/ml.

11. A composition including a barrier contraceptive device and at least one 5'-alkyl resorcinol and/or cannabinoid compound.

12. The composition of claim 11, wherein the compound is a cannabinoid selected from the group consisting of cannabinol derivatives, Δ8-THC derivatives, cannabichromene derivatives, cannabidiol derivatives, cannabigerol derivatives

13. The composition of claim 11, wherein at least one compound is IMG507, IMG508, IMG509, IMG510, or IMG511.

14. The composition of claim 11, wherein the barrier contraceptive device is a condom.

15. The composition of claim 11, wherein the barrier contraceptive device is a diaphragm.

Figure 1

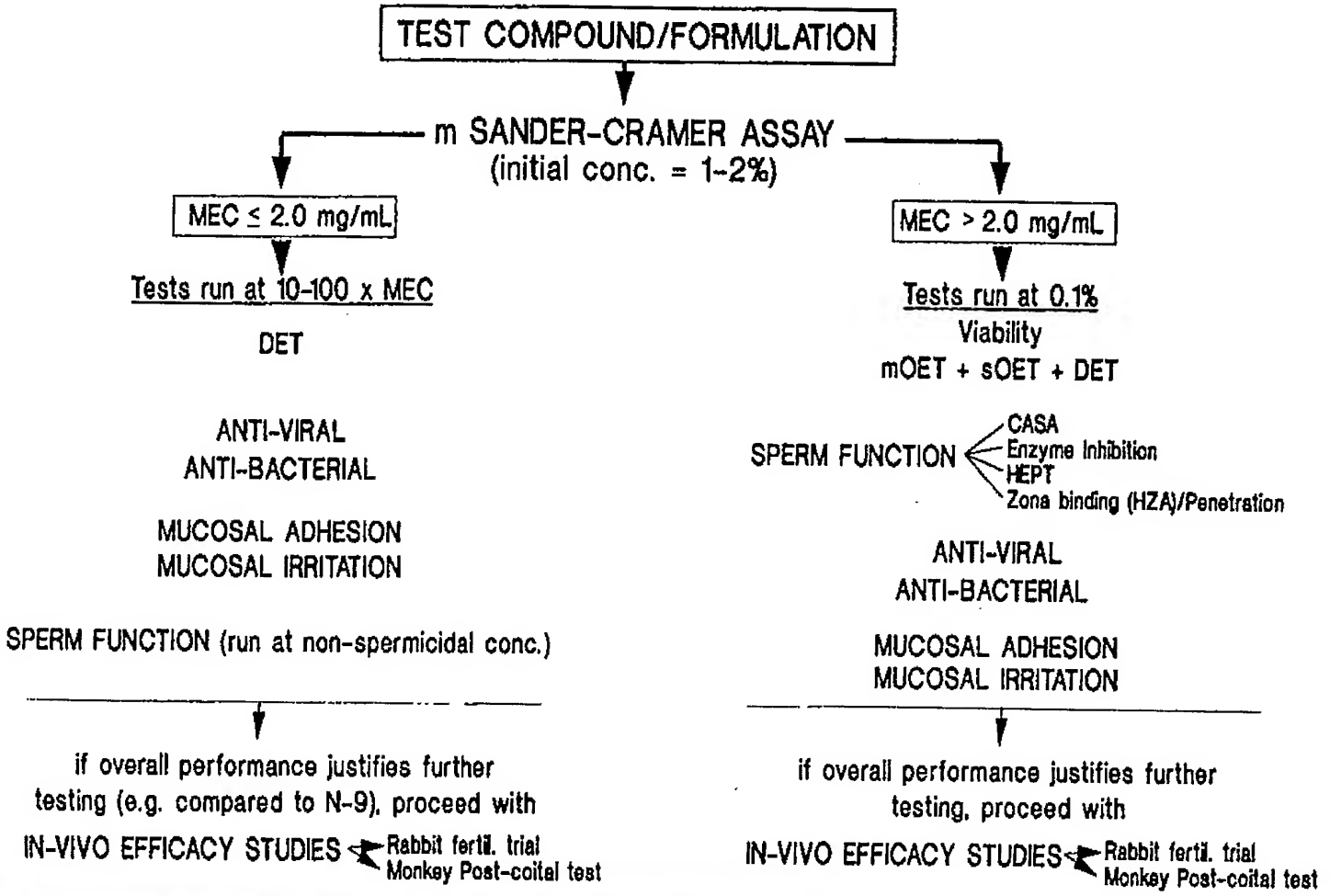


Figure 1. *Chemical Vaginal Contraceptives: Tentative preclinical screening algorithm.*
m: modified. MEC: minimum effective concentration. DET: double-end test. sOET: simultaneous one-end test. mOET: modified one-end test. CASA: computer-assisted semen analysis. HEPT: hamster-egg penetration test. HZA: hemizona assay.